IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant

Bertram L. Jacobs et al.

Serial No.

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Examiner

Guzo, Davis

Filed

April 19, 2001

Group Art Unit:

1636

For

VIRAL VECTORS HAVING REDUCED VIRULENCE

DECLARATION UNDER 37 C.F.R. § 1.132

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

October 14, 2003

Date of Deposit

Carmella L. Stephens

41.328

Attorney/Agent Name

PTO Registration No.

Signature 2. Sliphus

October 10, 2003

Date of Signature

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dear Sir:

follows:

- I, Bertram Jacobs of 1004 S. Wilson St., Tempe, AZ 85281, hereby declare as
- 1. I am a joint inventor of the invention described and claimed in the above-captioned patent application ("the present invention"), and hold the position of Professor at the Arizona State University in Tempe, Arizona. A copy of my Curriculum Vitae is attached as Exhibit A.

- 2. The present invention provides recombinant vaccinia virus having a deletion of the region encoding the C-terminal seven amino acids of the E3L gene product (E3LΔ7C). As disclosed in the above-captioned patent application, the mutations encompassed by the present invention are those which decrease, but do not abolish, binding of the mutant E3L gene product to dsRNA relative to the native E3L gene product.
- 3. I am a co-author of Brandt et al, 2001, *J. Virol.* 75(2):850-85 (hereinafter "Brandt") and thoroughly familiar with the disclosures therein. Brandt discloses a recombinant vaccinia virus lacking E3L (hereinafter "VVΔE3L") and a recombinant vaccinia virus comprising a truncated E3L gene that lacks nucleic acids encoding the carboxy terminal 26 amino acids (hereinafter "VVE3LΔ26C"). Brandt does not disclose whether the E3LΔ26C gene product binds dsRNA.
- 4. In accordance with the invention, in order to determine whether the dsRNA binding affinities of the E3LΔ7C gene product, the E3LΔ26C gene product, and wild type E3L gene product differ, respective preparations of total E3L protein were prepared by *in vitro* transcription and translation (paragraph 5 below), exposed to dsRNA (paragraph 6 below), and formation of nucleoprotein complexes was detected (paragraph 7 below).
- 5. Five micrograms of pBluescript or pGEM-5T plasmids containing wild type or mutant E3L DNA were linearized with HindIII, and T7 RNA polymerase (Promega) was used according to the manufacturer's specifications to transcribe RNA. After completion of the transcription reaction, samples were treated with DNase and extracted with phenol chloroform and chloroform. RNA was then precipitated from the samples with ethanol and resuspended in 20 μl of diethylpyrocarbonate-treated water. Aliquots of RNA (10 μl) were used in *in vitro* translation reactions (Promega). The translation reaction mixture contained 35 μl of nuclease-

treated rabbit reticulocyte lysate, 20 units of RNasin, 20 μ M amino acid mixture minus methionine, and 50 μ Ci of [35 S]methionine (1186 Ci/mmol; 1 Ci = 37 GBq). The reactions were carried out at 30° for 1.5 hr. After completion of the reaction, 15 μ l of the mixture was bound to poly(rl) poly(rC) - agarose.

- 6. Poly(rl) poly(rC)-agarose or reovirus dsRNA-agarose (Langland *et al.*, 1992) was washed three times in buffer A (150 mM KCl, 20mM HEPES, pH 7.5, 10% glycerol, 5mM MgOAc, 1mMDTT, 1mM benzamidine). [35S]methionine-labeled *in vitro* translation mixtures were added to the washed poly(rl) poly(rC)-agarose and incubated at 4° with occasional mixing for 1 hr. The agarose was then washed three times in buffer A. dsRNA-binding proteins were eluted from the agarose by adding an equal volume of 2X SDS/PAGE sample buffer and boiling for 3min. Proteins were separated by SDS/PAGE and visualized by autoradiography.
 - 7. Results for this study are depicted in Figure 1 below.

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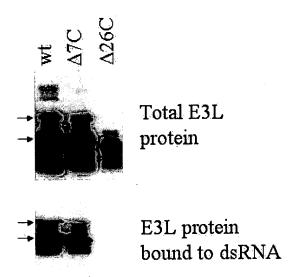
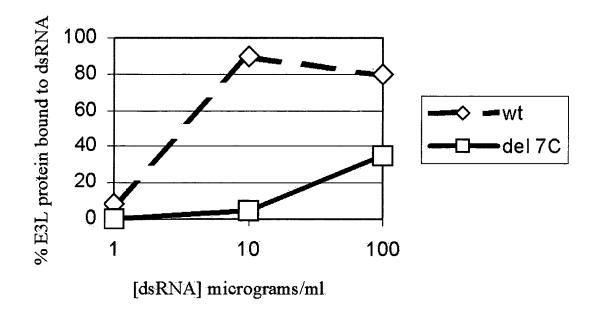


Figure 1. Vaccinia Virus E3L proteins bound to dsRNA

- 8. The upper panel of Figure 1 shows the total E3L protein produced by the respective E3L genes (arrows). The lower panel confirms prior observations that wild-type E3L protein binds dsRNA (left lane). Similarly, E3LΔ7C protein also binds dsRNA, albeit with a slightly reduced affinity (center lane). By contrast, E3LΔ26C protein did not form detectable nucleoprotein complexes when exposed to dsRNA (right lane).
- 9. The relative dsRNA-binding affinity of wild type E3L, the E3L Δ 26C of Brandt, and the E3L Δ 7C of the invention were tested. Increasing concentrations of soluble poly(rl) poly(rC) (0 to 100 μ g/ml) were incubated for 1 hr on ice with [35 S]methionine-labeled in vitro translation mixtures. Buffer A washed poly(rl) poly(rC)-agarose was then added to the mixture and incubated on ice for 1 hr. with occasional mixing. The agarose was then washed

three times in buffer A. Proteins were eluted from the agarose by adding an equal volume of 2X SDS/PAGE sample buffer and boiling for 3 min. Proteins were separated by SDS/PAGE and visualized by autoradiography. The relative amount of E3L proteins bound to poly(rl) poly(rC)-agarose were determined by scanning densitometry of the autoradiogram. The maximal binding of E3L proteins to poly(rl) and poly(rC)-agarose was in the presence of no soluble poly(rl) poly(rC) and was given the arbitrary value of 100%. The relative amount of E3L proteins bound to soluble (poly(rl) poly(rC) was obtained by subtracting the value of E3L proteins bound to poly(rl) poly(rC)-agarose from 100%.

10. Results for this study are depicted in Figure 2 below.



11. Figure 2 shows the percentage of E3L protein bound to dsRNA as a function of the concentration of the dsRNA-binding solution. No data points for E3L Δ 26C were plotted since no dsRNA binding could be detected at any concentration tested (i.e. 0-100 μ g/ml).

However, as demonstrated, the E3LΔ7C protein binds to dsRNA although with a lower affinity than wild type protein.

- 12. In conclusion, under the assay conditions used herein, there is a qualitative difference in the dsRNA binding properties of wild-type E3L protein and E3LΔ7C protein compared with E3LΔ26C protein. Specifically, both wild-type E3L protein and E3LΔ7C protein bind dsRNA while E3LΔ26C protein does not.
- 13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the above-captioned patent application.

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BERTRAM/JACOBS

Enclosure

EXHIBIT A A33781 072448.0308
PATENT

CURRICULUM VITAE

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Arizona State University
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EDUCATION

Ph. D., Biochemistry, June, 1981 University of California, Berkeley Dissertation advisor: E.E. Penhoet

Dissertation title: "The mechanism of assembly of vesicular stomatitis virus."

B.S., Biology, June, 1974 Rutgers University

Johns Hopkins University, 1968-1971

PROFESSIONAL EXPERIENCE

7/00-6/01 Distinguished Visiting Professor

Centro Nacional Biotechnologia, Madrid, Spain

Aventis, Pasteur, Toronto, Canada

Department of Microbiology and Molecular Genetics

University of Florida

8/96-7/00 Director

Graduate Degree Program in Molecular and Cellular

Biology

Arizona State University

8/96-present Professor

Department of Microbiology Arizona State University

8/90-8/96 Associate Professor

Department of Microbiology Arizona State University

EXHIBIT A	A33781 072448.0308 PATENT
6/91-1/92	Visiting Associate Research Professor Molecular Mechanisms of Carcinogenesis Laboratory Human Retrovirus Section National Cancer Institute Frederick Cancer Research Facility
8/85-3/90	Assistant Professor Department of Microbiology Arizona State University
6/84-8/85	Post-Doctoral Research Associate Department of Biological Sciences Section of Biochemistry and Molecular Biology University of California, Santa Barbara
1/81-6/84	Lecturer (50% time)/Post-Doctoral Research Associate (50% time) Department of Biological Sciences Section of Biochemistry and Molecular Biology University of California, Santa Barbara
9/75-1/81	NIH Pre-Doctoral Fellow Department of Biochemistry University of California, Berkeley
8/74-8/75	Research Assistant Department of Pathology Cornell University Medical College

PUBLICATIONS

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- 2. Jacobs BL, Penhoet EE. Assembly of vesicular stomatitis virus: distribution of the glycoprotein on the surface of infected cells. *J Virol*. 1982;44:1047-55.
- 3. Miyamoto NG, Jacobs BL, Samuel CE. Mechanism of interferon action. Effect of double-stranded RNA and the 5'-O-monophosphate form of 2',5'-oligoadenylate on the inhibition of reovirus mRNA translation in vitro. *J Biol Chem.* 1983;258:15232-7.
- 4. Jacobs BL, Samuel CE. Biosynthesis of reovirus-specified polypeptides: the reovirus s1 mRNA encodes two primary translation products. *Virology*. 1985;143:63-74.
- 5. Jacobs BL, Atwater JA, Munemitsu SM, Samuel CE. Biosynthesis of reovirus-specified polypeptides. The s1 mRNA synthesized in vivo is structurally and functionally indistinguishable from in vitro-synthesized s1 mRNA and encodes two polypeptides, sigma 1a and sigma 1bNS. *Virology*. 1985;147:9-18.

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- 7. Imani F, Jacobs BL. Inhibitory activity for the interferon-induced protein kinase is associated with the reovirus serotype 1 sigma 3 protein. *Proc Natl Acad Sci U S A*. 1988;85:7887-91.
- 8. Jacobs BL, Imani F. Histone proteins inhibit activation of the interferon-induced protein kinase by binding to double-stranded RNA. *J Interferon Res.* 1988;8:821-30.
- 9. Jacobs BL, Ferguson RE. The Lang strain of reovirus serotype 1 and the Dearing strain of reovirus serotype 3 differ in their sensitivities to beta interferon. *J Virol*. 1991;65:5102-4.
- 10. Watson JC, Chang HW, Jacobs BL. Characterization of a vaccinia virus-encoded double-stranded RNA- binding protein that may be involved in inhibition of the double-stranded RNA-dependent protein kinase. *Virology*. 1991;185:206-16.
- 11. Langland JO, Jacobs BL. Cytosolic double-stranded RNA-dependent protein kinase is likely a dimer of partially phosphorylated Mr = 66,000 subunits. *J Biol Chem*. 1992;267:10729-36.
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- 14. Lyubchenko YL, Gall AA, Shlyakhtenko LS, et al. Atomic force microscopy imaging of double stranded DNA and RNA. *J Biomol Struct Dyn.* 1992;10:589-606.
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- 17. Chang HW, Jacobs BL. Identification of a conserved motif that is necessary for binding of the vaccinia virus E3L gene products to double-stranded RNA. *Virology*. 1993;194:537-47.
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21. Denzler KL, Jacobs BL. Site-directed mutagenic analysis of reovirus sigma 3 protein binding to dsRNA. *Virology*. 1994;204:190-9.

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EXTRAMURAL RESEARCH SUPPORT

NIH/NIAID 1 U01 AI057303-01, July, 2003-2008, \$1,250,000/year entire project. "Development of a Safer Smallpox Vaccine" Pending

- NIH/NIAID R01 AI052347-01, July, 20023-2008, \$275,000 direct costs/year. "Role of the E3L and K3L genes in poxvirus pathogenesis" Pending.
- NIH/NIAID R21 AI052347-01, July, 2002-2003, \$200,000 direct costs/year. "Role of the E3L gene in poxvirus pathogenesis"
- NIH/NIAID R21 AI053457-01, July, 2002-2004, \$150,000/year, direct costs. "An Improved Vaccine for Protection Against Smallpox"
- NIH/NIAID R21 AI52787-01, July, 2002-2004, \$150,000/year, direct costs. "Mucosal Vaccination With A Vaccinia Virus-Based Vector"
- Dana Foundation, October 2001-2006, \$50,000/year total costs. "Pathogenic Mechanisms in Poxviruses"
- Wallace Foundation, December 2000-2003. \$100,000/year total costs. "Development of Viruses to Treat Cancer."
- Arizona Disease Control Research Commission, July,1, 1999-June 30, 2002. \$450,000. "Antisense mediated induction of apoptosis in cancer cells," PI.
- Arizona Disease Control Research Commission, July,1, 1999-June 30, 2001. \$500,000. "Viral vectors for treatment of brain cancer," Co-PI.
- Arizona Disease Control Research Commission, July 1, 1995-June 30, 1998. \$90,000. "Regulation of Programmed Cell Death in human cancer cells." #6-027. Principal investigator.
- American Cancer Society; 7/1/95-6/30/97. \$180,000. "Mechanism of transformation by inhibitors of the interferon system." VM-151. Principal investigator.
- National Institutes of Health; 4/1/95-3/31/99; \$950,000. "Role of E3L in poxvirus replication/IFN-resistance." R01 CA48654. Principal investigator. No-cost renewal 3/31/91-3/1/00.
- National Institutes of Health; 10/91-10/94; \$555,296. "Interaction of anti-HIV drugs with placental models." R01 AI32316. Co-principal Investigator.
- National Institutes of Health; 4/91-4/94; \$411,971. "Mechanism of action of interferon against HIV." R01 AI30349. Principal Investigator.
- National Institutes of Health; 5/88-5/93; \$493,369. "Control of the interferon-induced protein kinase." R29 CA48654. Principal Investigator.
- Arizona Disease Control Research Commission; 7/87-7/90; \$74,635. "Mechanism of induction of virus associated diabetes mellitus." Principal Investigator.
- American Diabetes Association; 7/87-7/90; \$69,710. "Mechanism of induction of virus associated diabetes mellitus." Principal Investigator.
- National Institutes of Health; 9/89-9/90; \$22,033. "Small Instrumentation Grant Program." Coprincipal Investigator.

INTRAMURAL RESEARCH SUPPORT

- Arizona State University Faculty Grant-in-aid; 1/95-12/95; \$6,000. "Regulation of programmed cell death in human cancer cells."
- Arizona State University Biomedical Research Fund; 1/89-1/90; \$8,413. "Characterization of a putative vaccinia virus inhibitor of interferon action."
- Arizona State University Biomedical Research Fund; 1/88-1/89; \$7,364. "Characterization of interferon-resistant viruses."

Arizona State University Biomedical Research Fund; 1/87-1/88; \$8,500. "The role of interferon in the etiology of insulin dependent diabetes mellitus."

Arizona State University Faculty Grant-in-aid; 1/87-1/88; \$3,000. "Molecular cloning of cDNA for an interferon-induced mRNA."

Arizona State University Research Fund; 1/86-1/87; \$8,740. "Purification of enzymes involved in the antitumor and antiviral effects of interferon."

Arizona State University Faculty Grant-in-aid; 1/86-1/87; \$3,000. "Molecular cloning of cDNA for an interferon-induced mRNA."

ASSOCIATIONS

American Society for Virology
American Society for Microbiology
American Association for the Advancement of Science

HONORS, EDITORIAL BOARDS, PROPOSAL REVIEW, etc.

Ad-hoc member, Virology Study Section, NIH, June, 2003

Invited Speaker, NIH Poxvirus Bioterrorism Research Meeting, Bethesda, MD. April, 2003.

"Replication competent attenuated strains of vaccinia virus as improved vaccines." at

"Replication competent, attenuated strains of vaccinia virus as improved vaccines." and "Role of a Z-DNA binding protein in poxvirus pathogenesis."

Arizona/Nevada Branch ASM, Keynote Speaker, February, 2003

University of Illinois 6th Annual Conference on New and Re-emerging Infectious Diseases, Keynote Speaker, April ,2003.

Invited Speaker, NIH Poxvirus Bioterrorism Research Meeting, Bethesda, MD. May 15-17, 2002. "Replication competent, attenuated strains of vaccinia virus as improved vaccines."

Member, US Inter-agency Smallpox Working Group, 2002

Member, Poxvirus Proteomics Review Panel, NIH, Dec. 2002

Ad-hoc member, Experimental Virology Study Section, NIH, Oct., 2002

Poxvirus expert, Biotechnology Enhancement Program Site Visit Team, VECTOR, Novosibirsk, Russia. July 20-25, 2002. Site visit is to audit a joint CDC/VECTOR grant, "Variola (smallpox) Genome Project."

Consultant, ISTC Project 1987, VECTOR, January 2003-

Member, Rapid Response to Bioterrorism Study Section, NIH, June, 2002

Chair, Poxvirus Pathogenesis Session of the International Poxvirus Symposium, Lake Placid, NY September 19-25, 2002.

Associate Editor, Virology, 1993-2002

Ad hoc reviewer for NSF, USDA, Canadian MRC, Journal of Biological Chemistry, Molecular and Cellular Biology, Virus Research, the Wellcome Trust.

RECENT INVITED LECTURES/SEMINARS

2003

ASU Sigma Xi Banquet, Keynote Speaker ASU President's Community Enrichment Program, Journeys of the Mind Department of Microbiology, St. Louis University

Arizona/Nevada Branch ASM, Keynote Speaker

University of Illinois 6th Annual Conference on New and Re-emerging Infectious Diseases, Keynote Speaker

2002

USAMRIID

Chair, Poxvirus Pathogenesis Workshop, International Poxvirus Symposium

NIH Poxvirus Research Meeting

Department of Chemistry, NAU

Department of Microbiology, University of Washington

Institute for Molecular Virology, Munich, Germany

Department of Microbiology and Immunology, University of Arizona School of Medicine 2001

Department of Microbiology, SUNY, Buffalo

Department of Cancer Biology, Cleveland Clinic

Department of Biology, MIT

Department of Microbiology, University of Western Ontario

Department of Microbiology and Molecular Genetics, University of Florida

2000

Centro Nacional Biotechnologia

TEACHING

Arizona State University, 1985-present

Honors: Nominated for College of Liberal Arts and Sciences Distinguished Teaching Award (1985/86, 1986/87, 1988/899, 1990/91). Selected for College of Liberal Arts and Sciences Distinguished Teaching Award, 1990/91. Graduate Student Council Outstanding Faculty Mentor, 1996.

MIC/PGS/JUS 394

HIV Disease in America. 3 Credits. Fall and Spring (1997-present). Lecturer and Faculty-in-charge. Class size, 70-80 students.

MIC 498

Molecular Techniques. 3 credits, Spring Semester (1991-2002). Team taught. Lecturer and Faculty-in-charge. Class size 6-12 students.

A33781 072448.0308 EXHIBIT A PATENT General Virology. 3 credits, Fall Semester (1985-2002). MIC 485 Sole lecturer and Faculty-in-charge. Class size 30-40. Virology Laboratory. 2 sections, 2 credits each, Fall MIC 486 Semester (1985-1989). Faculty-in-charge. Class size, appr. 10 students per section. ST: Topics in Molecular Virology. 3 credits, Spring MIC 494/598 Semester (1986-1991). Faculty-in-charge. Class size 10-15. S: Virology. 1 credit, Fall and Spring Semesters (1989-MIC 591 present). Faculty-in-charge. Class size 5-10. S: Molecular and Cellular Biology. 1 credit, Fall and MIC 591 Spring Semesters (1986-present). Team taught. Class size 5-10. S: Genetics. 1 credit, Fall and Spring Semesters (1985-MIC 591 2000). Team taught (with Zoology faculty). Class size 10-15. S: Enzymology. 1 credit, Fall and Spring Semesters (1986-MIC 591 1989). Team taught. Class size 5-10. Advanced Molecular and Cellular Biology. 3 credits, MCB 556 Spring Semester (1993, 1995). Team Taught. Class size 15-20. University of California, Santa Barbara, 1981-1984 Introductory Biology. 4 credits, Fall Semester (1982-1984). **BIO 11A** Team taught. Class size 300-400. Virology. 3 credits, Spring Semester (1981-1984). Faculty-**BIO 122** in-charge and sole lecturer. Class size 70-75.

University of California, Berkeley, 1980

BCM 102 General Biochemistry. 4 credits, Summer (1980). Faculty-

in-charge and sole lecturer. Class size 50.

Organic Chemistry review for students taking MCAT and GRE exams. Faculty-in-charge and sole lecturer. Class size

20.

GRADUATE COMMITTEES CHAIRED

NAME	DEGREE	CURRENT POSITION
Imani, Farhad	Ph.D., 8/89	Research Associate, The Johns Hopkins University School of Medicine, Baltimore, MD
Shearer, Michael	M.N.S., 6/87	Research Assistant, Southwest Biomedical Research Foundation, San Antonio, Texas
Watson, Julia	Ph.D., 12/90	Research Associate, Ribogene, Inc, Hayward, CA
Langland, Jeffrey	Ph.D., 12/90	Research Assistant Professor, Arizona State University
Chang, Cathy	Ph.D., 6/93	Research Scientist, Stratagene
Denzler, Karen	Ph.D., 6/94	Postdoctoral Research Associate, Mayo Clinic, Scottsdale
Shors, Scott	Ph.D., 6/94	Postdoctoral Research Associate, NIH, Bethesda, MD
Shors, Terri	Ph.D., 6/95	Assistant Professor, Department of Biology and Microbiology, University of Wisconsin,
Kibler, Karen	Ph.D., 12/97	Oshkosh Post-doctoral research associate, Mayo Clinic, Scottsdale
Zeman, Cameron	M.S., 12/97	Medical School, University of Iowa
Matt Banaszak	M.S., 12/98	Technician, VA Medical Center, Phoenix
Jennifer Biesterfeldt	M.S., 12/98	Technician, Mayo Clinic, Scottsdale
Kim Perkins	Ph.D., 12/99	Post-doctoral research associate, Mayo Clinic, Scottsdale
Sangeetha Vijaysri Teresa Brandt Maneesha Muralinath Stacy Frederick Kelly Trainor Chandra Mitnik	Ph.D., 8/01 Ph.D., 2001 Ph.D., 2003 Ph.D. candidate Ph.D. candidate Ph.D. candidate	Industry Industry

EXHIBIT A A33781 072448.0308
PATENT

Kevin HaunsPh.D. candidateMat PearcyPh.D. candidateGaralyn GentarraPh.D. candidate